View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Repositório Institucional UNIFESP

Respiratory Medicine (2005) **99**, S41–S48

ELSEVIER

respiratoryMEDICINE

Future perspectives in COPD

Bartolome Celli[a,*], Roger Goldstein[b], José Jardim[c], Katharine Knobil[d]

[a]*Caritas St. Elizabeth's Medical Center, Department of Medicine, Tufts University, Boston, USA*
[b]*Division of Respiratory Medicine, Faculty of Medicine, University of Toronto, c/o West Park Healthcare Centre 82 Buttonwood Avenue, Toronto, Ont., Canada M6M 2J5*
[c]*Department of Pulmonary Diseases, Federal University of Sao Paulo, Rua Botucatu, 740–3° Andar, Pneumologia (Respiratory Division) Unifesp, 04023-060, Sao Paulo, Brazil*
[d]*Respiratory Medicines Development Center, GlaxoSmithKline, Research Triangle Park, NC, USA*

Received 5 August 2005; accepted 7 September 2005

KEYWORDS
BODE;
COPD;
Fluticasone propionate;
International COPD genetics network;
Oxidative stress;
Pulmonary rehabilitation;
Systemic inflammation;
Salmeterol;
Tiotropium;
TORCH;
UPLIFT

Summary The pathophysiology of chronic obstructive pulmonary disease (COPD) is complex. The development of a multidimensional index—such as the BODE index—provides a means of classifying patients with COPD that also correlates with their prognosis. The individual components of the BODE index—body mass index (B), airflow obstruction (O) dyspnoea (D) and exercise capacity (E)—incorporate the pulmonary as well as the systemic effects seen in patients with COPD. Recent research has focussed on examining these impairments (including those of metabolism and inflammation) more carefully, and determining the effects of treatment on both the systemic and physiological aspects of COPD.

Ongoing research initiatives by the public and private sector will contribute to our understanding of the disease processes underlying COPD, our understanding of the benefits associated with commonly used pharmacotherapies, as well as laying the foundations for the development of new agents and therapeutic tools. Advances in the use of pharmacotherapy have been mirrored by research to better define the benefits associated with pulmonary rehabilitation. Many questions remain to be answered, but a comprehensive approach is now considered essential to the life-long management of COPD, and will undoubtedly reduce the considerable socio-economic burden of COPD.
© 2005 Elsevier Ltd. All rights reserved.

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; LVRS, lung-volume-reduction surgery; MMRC, modified Medical Research Council; MTCSA, mid-thigh cross-sectional area; TNF-α, tumor necrosis factor-alpha; TLC, total lung capacity; TORCH, TOwards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium

*Corresponding author. Tel.: +1 617 789 2554; fax: +1 617 562 7756.
E-mail address: bcelli@copdnet.org (B. Celli).

0954-6111/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2005.09.014

Introduction

According to the 2004 update of the WHO world health report, chronic obstructive pulmonary disease (COPD) was the fifth most common cause of death in 2002 (4.8% of deaths)—only ischaemic heart disease (12.6% of deaths), cerebrovascular disease (9.7%), lower respiratory infections (6.8%) and HIV/AIDS (4.9%) were more common causes of death worldwide.[1] Clearly therefore, COPD imposes a huge socio-economic burden on both the individual and society. Novel modes of therapy will have to be developed, and our current array of treatments utilised to their fullest extent, to further reduce the chronic burden of this disease on the patient, and ultimately, improve long-term survival. Examples include more efficient smoking cessation strategies, targeted pharmacological therapies, and the incorporation of pulmonary rehabilitation into the life-long management of individuals with chronic respiratory disease.[2] Furthermore, the initiation of large pharmaceutical trials specifically designed to evaluate disease modification or a survival advantage will have a major impact on our understanding of COPD and its treatment.[3] It is clear that chronic airflow limitation is only the most obvious manifestation of a disease that is also characterised by systemic inflammation,[4] oxidative stress[5] and muscular weakness.[6] Our better understanding of how these and other disease processes impact on well-being and survival will almost certainly lead to better outcomes.

Towards a better appreciation of the pervasive nature of COPD

The physiological hallmark typically used now to define COPD—a reduction in forced expiratory volume in 1 s (FEV_1)—underscores the importance of progressive airway obstruction in this disease.[7] However, COPD clearly has complex pathophysiology, and other factors must be considered in evaluating its effect on patients. The BODE index, published in 2004,[8] is a multidimensional scoring system designed to this effect. The index was developed by examining a cohort of 207 patients with COPD for factors predictive of death. Four factors were identified—body mass index (B), airflow obstruction (O), dyspnoea (D) and exercise capacity (E). Measurements of each variable were assigned scores (Table 1), such that summing the scores together would give an index of disease severity—the BODE index. This scoring is strongly predictive, not only for respiratory death, but also for death from any cause,[8] and its scoring by quartiles is more predictive of survival than the three-stage American Thoracic Society (ATS) spirometric staging (Fig. 1).[9] The predictive power of the BODE index arises from incorporating four domains that are strongly informative for different aspects of the health of patients with COPD.

Clearly, airflow limitation is critical in evaluating COPD. FEV_1 has long been known to reflect underlying airflow limitation in COPD, and is a good marker for disease progression.[7] However, FEV_1 measurement is not a good surrogate for measurement of dyspnoea—the predominant symptom in COPD, and a stronger predictor of mortality than the FEV_1.[10,11] Dyspnoea can be reliably and accurately assessed using unidimensional or multidimensional scales.[7]

Over the previous decade, there has been an increasing appreciation of the importance of the systemic manifestations of COPD.[12] These include muscular weakness and alterations in body mass index (BMI), both of which are related to survival in patients with COPD.[13,14] The effect of nutritional depletion on survival was demonstrated in a study published by Schols et al. in 1998.[13] In this study,

Table 1 The BODE index—four variables identified as being predictive of survival in patients with COPD, and the values (0–3) assigned to each variable by category.[8]

Variable	Points on the BODE index			
	0	1	2	3
B—Body mass index (kg/m^2)*	>21	$\leqslant 21$	—	—
O—FEV_1 (% of predicted)†	$\geqslant 65$	50–64	36–49	$\leqslant 35$
D—Distance walked in 6 min (m)	$\geqslant 350$	250–349	150–249	$\leqslant 149$
E—MMRC dyspnoea scale (score)	0–1	2	3	4

FEV_1, forced expiratory volume in 1 s; MMRC, modified Medical Research Council.

*Values for body mass index are 0 or 1 owing to the inflection point in the inverse relationship between survival and body mass index at a value of 21 kg/m^2.

†FEV_1 categories are based upon stages identified by the American Thoracic Society.

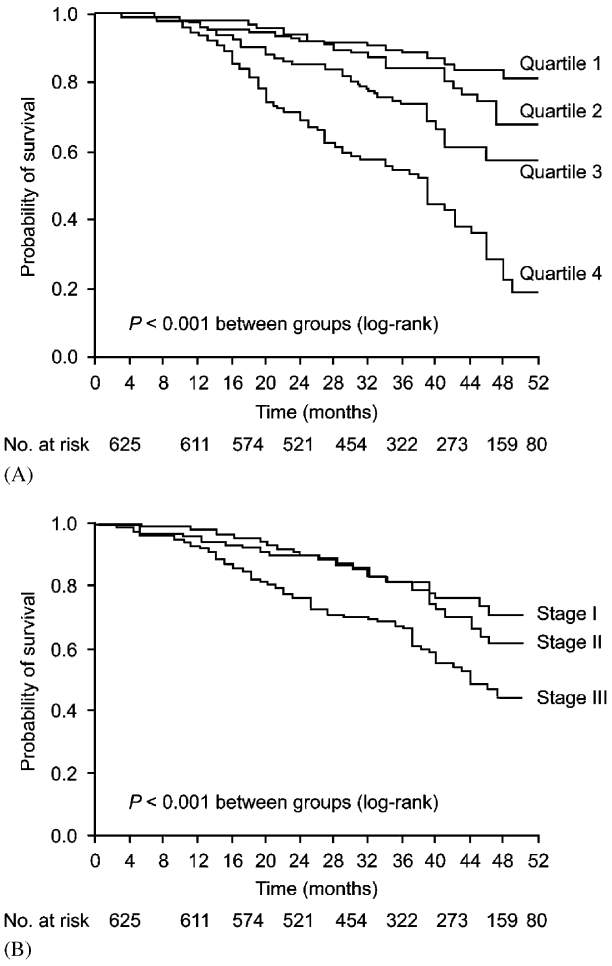

Figure 1 (A) Kaplan–Meier survival curves for the four quartiles of the BODE index and (B) for the three stages of severity of COPD as defined by the American Thoracic Society.[8]

stratifying patients ($N = 400$) with COPD into BMI quintiles revealed a threshold value for BMI of 25 kg/m^2, below which there was a clear increase in the risk of mortality.[13] Patients with COPD also have weak respiratory and peripheral muscles,[6] with muscular weakness being linked to reduced survival.[14] Indeed, Marquis et al.[14] in 2002, showed that mid-thigh cross-sectional area (MTCSA) is strongly predictive of mortality, and has a particularly strong impact on survival in patients with an $FEV_1 < 50\%$. Furthermore, reduced muscular strength is likely a reflection of patient functional or exercise capacity, and can be measured using the 6-min walk test. Pinto-Plata et al.[15] showed that, during a 2-year observation of 198 patients with severe COPD, there were greater reductions in the distance walked in 6 min among the patients who died. In fact, the 6-min walk test predicted mortality better than FEV_1 measurements.

Although muscular weakness (MTCSA), exercise capacity (6-min walk test) and BMI are interrelated, and are likely to share some of the underlying determinants, they indicate different aspects of the pathophysiology of COPD, and are independent predictors of mortality.[13,15–17] In particular, the 6-min walk test contains a degree of sensitivity not provided by measurements of BMI. The inclusion of both BMI and 6-min walk test measures in the BODE index, ensures that the final BODE score strongly reflects the pathophysiological effects of COPD on the patient.[8]

New paradigms in COPD therapy

Targeting lung hyperinflation in COPD

Static and dynamic lung hyperinflation—common physiologic derangements in COPD—are important determinants of exertional dyspnoea,[18] with emerging evidence linking hyperinflation to mortality. In a 2004 study of 689 patients with stable COPD by Casanova et al., lung hyperinflation was a significant predictor of mortality. Inspiratory capacity (IC) was used as an indirect measure of hyperinflation, because in the absence of a change in the total lung capacity (TLC), a decrease in IC indicates an increase in end-expiratory lung volume or hyperinflation. Those patients with an IC/TLC ratio >0.25 had significantly greater cumulative survival (all cause or respiratory failure) over the course of 4 years (Fig. 2), compared with an IC/TLC $\leqslant 0.25$ ($P < 0.0001$).[19] If hyperinflation is truly associated with increased mortality, then targeting this physiologic abnormality may prove a useful target for future treatment paradigms.

Bronchodilators, both short- and long-acting, have been shown to reduce hyperinflation in patients with COPD. In a trial reported by Celli et al.[18] tiotropium was associated with significant ($P < 0.05$) reductions in inspiratory capacity and thoracic gas volume over 4 weeks. Similar results have been shown with the long-acting β_2-agonist salmeterol.[20]

Lung-volume-reduction surgery (LVRS) is another means of reducing hyperinflation, and the relationship between LVRS and survival was examined recently in the National Emphysema Treatment Trial. This study examined the effects of LVRS usual medical care (pulmonary rehabilitation) in 1218 patients with severe emphysema.[21] Subgroup analysis showed that surgery had the greatest survival benefit for those patients with both predominantly upper-lobe emphysema and low baseline exercise

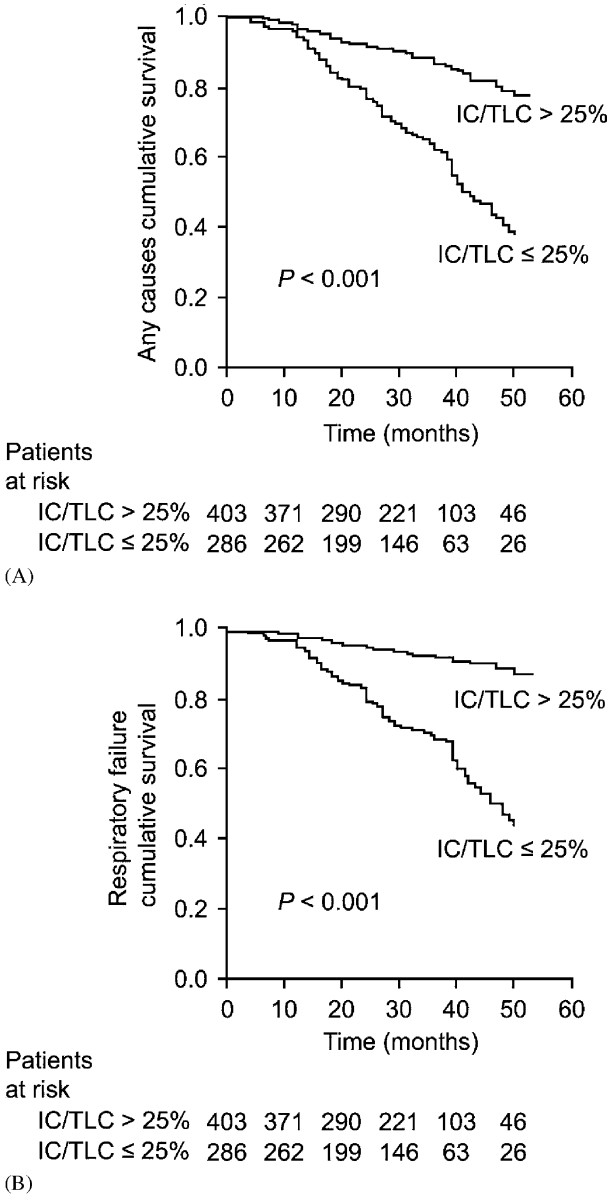

Figure 2 Cumulative survival (4-year) of patients with stable COPD and an inspiratory capacity/total lung capacity (IC/TLC) >0.25, versus patients with stable COPD and an IC/TLC$\leqslant 0.25$. Kaplan–Meier survival curves for (A) all causes and (B) respiratory failure.[19]

capacity. Therefore, while LVRS can prolong survival in COPD, this beneficial outcome is restricted to a carefully selected group of patients.

Targeting the systemic effects of COPD—molecular insights

The use of long-term oxygen therapy has been shown to improve life expectancy in COPD.[22,23] This therapy does not modify the degree of airflow limitation and therefore provides hard evidence that it is not absolutely necessary to change lung function to improve outcomes in COPD. Indeed, more recent studies have provided a molecular basis for, and insight into, the benefits associated with therapies that are directed at the systemic manifestations of the disease, rather than at altering lung function.

A number of studies have demonstrated that patients with COPD have systemic metabolic defects. Maltais et al. examined arterial lactic acid concentrations and the oxidative capacity of skeletal muscle during exercise in nine patients with COPD. Compared with control subjects, patients with COPD had significantly ($P<0.0005$) reduced levels of oxidative enzymes, as well as significantly ($P<0.0005$) increased levels of lactic acid.[24] Sauleda et al.[25] also showed that patients with chronic respiratory failure and COPD have increased respiratory-muscle mitochondrial cytochrome oxidase activity relative to normal subjects. Taken together, these results suggest that, compared with normal subjects, muscular tissue in patients with COPD is fundamentally less able to process metabolic precursors and waste products and, consequently, is more readily subjected to metabolic oxidative stress during exercise. These observations are clearly related to the respiratory and peripheral muscular weakness experienced by patients with COPD. Of note, such molecular observations have a very real bearing on the outcome of the patient—in 2004, Montes de Oca et al.[26] published the results of a study showing a relationship between markers of oxidative stress (nitrite, nitrate and nitrotyrosine) and the BODE index.

Further evidence of the systemic consequences of COPD is provided by the unexplained weight loss that is observed in 30–50% of patients with COPD—a contributory cause of mortality.[27] This weight loss has been shown to be associated with levels of tumour necrosis factor-alpha (TNF-α)—an inflammatory mediator shown to cause cachexia in laboratory animals.[28] A study published by Di Francia et al.[29] in 1994 examined the relationship between serum TNF-α levels and body weight in 30 patients with stable COPD. Those patients with a mean body weight 81% of normal had 10-fold higher levels of TNF-α (70.2 pg/mL), compared with patients who had a mean body weight of 121% of normal (TNF-$\alpha = 6.7$ pg/mL; $P = 0.0001$). Hence, TNF-α is clearly a contributory factor to weight loss, muscular weakness and reduced BMI in these patients. In a different study, Sin et al.[30] demonstrated that fluticasone propionate substantially (71%; $P = 0.039$) reduces the levels of C-reactive protein—a well-known marker of inflammation. This observation is extremely important because it

raises the possibility that we could modify some, if not all, of the markers of systemic inflammation, and, if confirmed, could open new avenues of therapy.

It will become increasingly important in the future to develop new treatment paradigms that make full use of our knowledge of the pathophysiology of COPD, so that we are better able to treat the effects of this disease and assess how beneficial these treatments are for the patient.

New pharmaceutical industry initiatives for COPD

With expansion of our knowledge of the pathophysiology of COPD, we are better able to characterise and manage patients with this disease. Paralleling such advances are new means of identifying those at risk of COPD, as well as new treatments to modify the course of this condition.

The international COPD genetics network

Initiatives are underway to clarify disease mechanisms, permitting better phenotypic characterisation and, ultimately, encouraging the discovery and development of new disease-modifying drugs. One of the most important of these initiatives—The International COPD Genetics Network (sponsored by GlaxoSmithKline)—has enrolled 3500 patients (and in many cases their siblings) across 10 investigative sites, into a family-based study, to identify susceptibility genes for COPD. Extensive genetic and phenotypic data have been collected from study participants so as to better define the manifestations of COPD and to help characterise intermediate phenotypes. Analysis of phenotypic and genetic data should assist with the identification of patients at risk of COPD and the prediction of patient response to treatment.

As part of the Genetics Network initiative, new tools to characterise the anatomical and mechanistic changes associated with COPD are being developed. For example, patients in the network will undergo high-resolution computed tomography scans, the data being used to validate this technique and also to provide greater discrimination of the different phenotypic aspects of COPD (e.g. airway disease versus parenchymal disease), so that the effects of treatment can be more precisely defined. This could prove important in demonstrating efficacy of treatment when changes in lung function as measured by spirometry may not be detectable. Other tools in development include the use of inhaled hyperpolarised gas to aid in producing three-dimensional images of the lung. These images can be used to provide important measurements of lung dimensions, so that through the comparison of multiple images from the same patient over time, a more dynamic assessment of their disease progression and the effect of treatment are obtained.

Defining the benefits of COPD pharmacotherapy—key trials

Randomised clinical trials have established the benefits of long-term home oxygen therapy on survival in COPD.[31] While the benefits of pharmacotherapy in reducing airflow limitation and exacerbations have been well established in COPD, improvements in survival and in the rate of decline in FEV_1 are now the subject of important prospective trials.

TORCH—TOwards a revolution in COPD health

TORCH is a landmark multicentre, randomised, double-blind, parallel-group, placebo-controlled study, which is designed to establish the effect on survival of fluticasone propionate (steroid) and salmeterol (long-acting β_2-agonist) individually or in combination.[3] The primary end point is all-cause mortality; secondary end points are COPD morbidity relating to rate of exacerbations, and health status assessed using the St. George's Respiratory Questionnaire.[32] The trial was initiated in 2000, and results are expected in 2006. The data from this large, randomised trial in over 6000 patients from 42 countries, will prospectively examine findings from previous observational studies and post hoc analyses, which demonstrated improvement in survival with inhaled steroids and long-acting β_2-agonists in patients with COPD.

UPLIFT—understanding potential long-term impacts on function with tiotropium

UPLIFT is a multicentre, randomised, double-blind, parallel-group, placebo-controlled study, that is designed to establish whether tiotropium can reduce the rate of lung function decline (pre and post-bronchodilator FEV_1 from 30 days to study completion), health status and exacerbation frequency in patients with COPD.[33] The trial was initiated in 2003 and the results are expected in 2008. The data from this large randomised trial in over 6000 patients from 35 countries is important because, to date, no pharmacological intervention has conclusively shown such benefits.

The results of both TORCH and UPLIFT are eagerly awaited, as they will undoubtedly enhance our understanding of the long-term effect of treatment on the natural history of COPD.

The future of pulmonary rehabilitation

Pulmonary rehabilitation—early myths refuted

The emergence of pulmonary rehabilitation over the past 15 years as a gold standard of care, and its prominent placement in recent COPD guidelines has come following the refutation of a number of myths in the medical community. These myths include, firstly, the assumption that little can be done to address the physiological impairments of COPD; secondly, that since pulmonary rehabilitation has little effect on airflow limitation it cannot have appreciable beneficial effect on the patient; thirdly, that since their condition is largely self-induced through smoking, nothing should be done to assist these patients; and finally, that in the latter stages of COPD the prognosis is invariably poor. These misconceptions have given way to a more comprehensive approach to the treatment of these patients, and the realisation that even severely affected patients can still enjoy appreciable survival as well as health-related quality of life.[2]

Other prevailing myths were that comorbidities are a contraindication for pulmonary rehabilitation; that non-physicians have a very limited role; and that the goals of rehabilitation were best defined by healthcare professionals. On the contrary, the appropriate management of the patient's comorbidities reduces their effect on exercise intolerance, and pulmonary rehabilitation is best administered by an inter-disciplinary team, incorporating a collaborative approach where the patient is integrally involved in determining their own rehabilitation intervention.[2]

The perception that pulmonary rehabilitation is expensive was one of the easier myths to refute. Two recent studies published by Bourbeau et al.[34] in 2003 and Griffiths et al.[35] in 2000, showed that pulmonary rehabilitation significantly decreases the use of health care services. In the former study, patients with advanced COPD were randomised to receive usual care ($n = 95$) or a home-based programme of education and self-management ($n = 95$) once per week for 2 months, with 1 year of follow-up. Compared with usual care, patients receiving the education programme had a 39.8% ($P = 0.01$) reduction in hospital admissions for exacerbations and a 57.1% ($P = 0.01$) reduction in admissions for other health problems.[34] In addition, emergency department visits and unscheduled physician visits were reduced by 41.0% ($P = 0.02$) and 58.9% ($P = 0.003$), respectively. Similar results were seen in a study by Griffiths et al.[35] In this study, 200 patients with disabling COPD ($FEV_1 < 60\%$ of predicted) were assigned to a 6-week rehabilitation programme or standard medical management, and were followed up for 1 year. Those patients receiving rehabilitation spent 50% less time in hospital (mean of 10.4 days versus 21.0 days; $P = 0.022$) and had fewer primary care home visits (1.5 versus 2.8 visits; $P = 0.037$) than the standard care group.[35] In this trial the direct costs of pulmonary rehabilitation were more than offset by reductions in subsequent healthcare utilisation.

Pulmonary rehabilitation—where to now?

In addition to the benefits already described, indirect evidence suggests that pulmonary rehabilitation can extend survival, since dyspnoea,[11] quality of life[36] and functional status[37] correlate with survival, and it is clear that pulmonary rehabilitation can provide improvements in these parameters.[2] Future research will focus on definitively establishing whether rehabilitation can improve survival, and developing the means to maintain the benefits of rehabilitation—likely to depend on behavioural changes. The other important goal in the management of COPD, is to increase the autonomy of patients with chronic respiratory disease, through enhanced physical, social and psychological function.

It will also be important to expand the use of pulmonary rehabilitation, by providing increased access to rehabilitation programmes. This can be achieved by increasing the provision of resources and services, by allowing patients to access programmes earlier and more easily, and by further developing the content of pulmonary rehabilitation programmes. We should also extend the use of pulmonary rehabilitation to include other forms of chronic respiratory illness.

Conclusions

While many questions remain unanswered, recent years have witnessed an explosion in our knowledge of how to characterise and treat patients with COPD. The focus of future research must be to further our understanding of the molecular basis of

COPD and to determine how this relates to the gross pathophysiological defects seen in these patients. New treatments and the wider application of individually designed treatments, such as pulmonary rehabilitation, remain an important focus.

References

1. The world health report 2004—changing history. 2005. Available at: http://www.who.int/whr/2004/en/
2. Pulmonary rehabilitation. *Thorax* 2001;**56**:827–34.
3. Vestbo J. The TORCH (towards a revolution in COPD health) survival study protocol. *Eur Respir J* 2004;**24**:206–10.
4. Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003;**58**:752–6.
5. Couillard A, Maltais F, Saey D, et al. Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;**167**:1664–9.
6. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2001;**33**: S662–70.
7. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
8. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350**:1005–12.
9. Celli B, Snider GL, Heffner J, et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 1995;**152**: S77–S120.
10. Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. *Chest* 1989;**96**:1247–51.
11. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;**121**:1434–40.
12. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. *Chest* 2002;**121**:127S–30S.
13. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**: 1791–7.
14. Marquis K, Debigare R, Lacasse Y, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;**166**: 809–13.
15. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;**23**: 28–33.
16. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996;**9**:431–5.
17. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**: 1856–61.
18. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest* 2003;**124**:1743–8.
19. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**171**:591–7.
20. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;**24**:86–94.
21. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;**348**: 2059–73.
22. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981;**1**:681–6.
23. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980;**93**:391–8.
24. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996;**153**:288–93.
25. Sauleda J, Garcia-Palmer F, Wiesner RJ, et al. Cytochrome oxidase activity and mitochondrial gene expression in skeletal muscle of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**: 1413–7.
26. Montes de Oca M, Torres SH, De Sanctis JB, Talamo C, Celli BR. Systemic inflammation: relation between oxidative stress and the multiple component staging system BODE in COPD patients. *Am J Respir Crit Care Med* 2004;**A616**.
27. Wilson DO, Rogers RM, Hoffman RM. Nutrition and chronic lung disease. *Am Rev Respir Dis* 1985;**132**:1347–65.
28. Tracey KJ, Wei H, Manogue KR, et al. Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. *J Exp Med* 1988;**167**:1211–27.
29. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;**150**: 1453–5.
30. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;**170**: 760–5.
31. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting. *Intern Med J* 2001;**31**:448–54.
32. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;**145**:1321–7.
33. Decramer M, Celli B, Tashkin DP, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: The Uplift trial. *J Chronic Obstructive Pulmonary Dis* 2004;**1**:303–12.

34. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;**163**:585–91.
35. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;**355**:362–8.
36. Domingo-Salvany A, Lamarca R, Ferrer M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;**166**:680–5.
37. Bowen JB, Votto JJ, Thrall RS, et al. Functional status and survival following pulmonary rehabilitation. *Chest* 2000; **118**:697–703.